We claim:

1. A method of inducing apoptosis in a target cell, comprising:

inhibiting a cell fate determining function of a Notch protein in the target cell at a time when the cell is undergoing differentiation, which induces the target cell to undergo apoptosis.

2. The method of claim 1, wherein the target cell is a tumor cell characterized by:

(a) increased expression of the Notch protein; or

(b) increased Notch activity or expression, relative to Notch activity or expression in a same tissue type that is not neoplastic.

3. The method of claim 2, wherein the Notch protein is Notch-1.

4. The method of claim 2, wherein the Notch protein is Notch-2.

5. The method of claim 2, wherein the tumor cell is:

(a) selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy; and

(b) is a tumor cell in a subject.

6. The method of claim 1, further comprising inducing differentiation of the target cell so that inhibition of the function of Notch induces apoptosis of the cell.

7. The method of claim 6, wherein inducing differentiation of the target cell comprises administering an effective amount of a differentiation inducing agent.

8. The method of claim 7, wherein the differentiation inducing agent comprises an agent selected from the group of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachinodate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof.

9. The method of claim 8, wherein the agent is a polar hybrid compound.

10. The method of claim 9, wherein the polar hybrid compound is hexamethylene bisacetamide (HMBA).

11. The method of claim 1, wherein inhibiting the cell fate determining function of Notch protein comprises inhibiting expression of Notch protein in the target cell.

12. The method of claim 11, wherein inhibiting expression of Notch protein comprises exposing the cell to an effective amount of an antisense molecule that specifically blocks expression of Notch protein.

13. The method of claim 12, wherein the antisense molecule includes at least six contiguous nucleotides of a sequence that is complementary to at least a portion of an RNA transcript of a *Notch* gene, and is hybridizable to the RNA transcript.

14. The method of claim 13, wherein the *Notch* gene is *Notch*-1.

15. The method of claim 13, wherein the *Notch* gene is *Notch*-2.

16. The method of claim 13, wherein the antisense molecule comprises at least six contiguous nucleotides from the group consisting of SEQ. ID. NOS. 6, 8, or 11.

17. The method of claim 11, wherein inhibiting the function of Notch protein comprises exposing the cell to a molecule which antagonizes the function of the Notch protein.

18. The method of claim 17, wherein the molecule which antagonizes the function of Notch protein comprises an antibody that specifically binds to Notch, or a portion of the antibody containing a binding domain that specifically binds to Notch.

19. An antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of a differentiation inducing agent.

20. The antibody of claim 19, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

21. A hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

22. The method of claim 18, wherein the antibody is an antibody against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent.

23. The method of claim 22, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

24. The method of claim 18, wherein the Notch protein is Notch-2.

25. A method of inducing apoptosis in a tumor cell that is characterized by increased expression of a Notch protein, comprising:

inducing differentiation of the tumor cell by exposing the tumor cell to a differentiation inducing agent; and

interfering with the Notch function or expression in the tumor cell, at a time during differentiation when the Notch is required to prevent apoptosis, by administering a molecule that specifically interferes with the Notch function or expression.

26. The method of claim 25, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch-1 protein.

27. The method of claim 25, wherein administering the molecule comprises administering an antibody which specifically binds to the Notch-1 protein and interferes with Notch-1 function.

28. The method of claim 25, wherein exposing the tumor cell to a differentiation inducing agent comprises exposing the tumor cell to a differentiation inducing amount of an agent from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachindonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof that induce differentiation of the tumor cell.

29. The method of claim 25, wherein the tumor cell is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

30. The method of claim 25, wherein the tumor cell is a hematopoietic malignancy or a cervical cancer in which Notch-1 expression is increased.

31. The method of claim 25, wherein:

exposing the tumor cell to a differentiation inducing agent comprises exposing the tumor cell to a differentiation inducing amount of hexamethylene bisacetamide (HMBA); and

the tumor cell is in a subject, to whom the differentiation inducing agent is administered in a therapeutically effective amount.

32. The method of claim 25, wherein administering the molecule comprises:

administering a therapeutically effective amount of an antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent; and

subsequently administering a therapeutically effective amount of a differentiation inducing agent.

33. The method of claim 20, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch-2 protein.

34. The method of claim 32, wherein the monoclonal antibody is selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

35. The method of claim 25, wherein the tumor cell is in a subject, to whom the differentiation inducing agent and monoclonal antibody are administered separately, in a therapeutically effective amount.

36. A method of stimulating differentiation in a target cell, comprising:

administering a therapeutically effective amount of a differentiation agent; and

administering a therapeutically effective amount of an antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent.

37. The method of claim 36, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655; and the target cell is a tumor cell characterized by increased expression of Notch-1 protein.

38. The method of claim 36, wherein the target cell is characterized by increased Notch-1 activity or expression, relative to Notch-1 activity or expression in a same tissue type that is not neoplastic.

39. The method of claim 36, wherein the target cell is a tumor cell in a subject.

40. The method of claim 36, where the target cell is selected from the group consisting of a cervical cancer cell, a breast cancer cell, a colon cancer cell, a melanoma cell, a seminoma cell, a lung cancer cell, and a hematopoietic malignancy cell.

41. The method of claim 36, wherein in the differentiation inducing agent comprises an agent selected from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivative, hormones, hormone antagonisits, and biologic promotors of differentiation, and derivatives thereof.

42. The method of claim 36, wherein in the differentiation inducing agent is a polar hybrid compound. or HMBA.

43. The method of claim 42, wherein the polar hybrid compound is hexamethylene bisacetamide (HMBA).

44. The method of claim 36, wherein stimulating differentiation comprises stimulating terminal differentiation followed by apoptosis.

45. The method of claim 36, wherein stimulating differentiation of the target cell also inhibits a function of Notch-1 which induces apoptosis of the cell.

46. A method of treating a tumor in a subject, wherein the tumor is characterized by an overexpression of Notch protein in cells of the tumor, the method comprising:

administering to the subject an amount of a differentiation inducing agent sufficient to induce at least partial differentiation of cells in the tumor;

administering to the subject a therapeutically effective amount of a molecule that specifically interferes with Notch expression.

47. The method of claim 46, wherein the molecule is selected from the group consisting of an antibody to Notch-1 and an oligonucleotide that specifically interferes with expression of Notch-1 in cells of the tumor.

48. The method of claim 47, wherein the molecule is an antisense oligonucleotide selected from the group of SEQ. ID. NOS. 2, 4 or 7, and the differentiation inducing agent is HMBA.

49. The method of claim 46, wherein the molecule is selected from the group consisting of an antibody to Notch-2 and an oligonucleotide that specifically interferes with expression of Notch-2 in cells of the tumor.

50. The method of claim 46, wherein the molecule is the monoclonal antibody of claim 15, and the differentiation inducing agent is HMBA.

51. The method of claim 46, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655, and the differentiation inducing agent is HMBA.

52. A method of diagnosing and staging tumor cells which overexpress Notch relative to Notch levels in a same tissue type that is not neoplastic, comprising using an antibody generated against Notch.

53. The method of claim 52, wherein the method comprises using an antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular

epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent for immunostaining.

54. The method of claim 53, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

55. The method of claim 53, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

56. The method of claim 52, wherein the tumor is a cervical cancer or the tumor cells are in a Pap smear.

57. A method of generating an antibody using the plasmid pLD101.

58. The method of claim 57 wherein the antibody is:

a monoclonal antibody; or

a monoclonal antibody that recognizes Notch-1 EGF- repeats 11-12.

59. A pharmaceutical composition comprising a differentiation inducing agent and a molecule that specifically interferes with expression of, or a cell fate determining function of, Notch protein, the agent and molecule being present in an antineoplastic effective amount.

60. The pharmaceutical composition of claim 59, wherein:

the molecule comprises an oligonucleotide comprising at least six nucleotides from a sequence complementary to at least a portion of an RNA transcript of a *Notch* gene, and is hybridizable to the RNA transcript; and

the differentiation inducing agent is selected from the group consisting of: retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof that induce differentiation.

61. The pharmaceutical composition of claim 59, wherein the molecule comprises an oligonucelotide selected from the group of SEQ. ID. NOS. 6, 8, or 11.

62. The pharmaceutical composition of claim 60, wherein the molecule is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal

antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

63. A pharmaceutical composition comprising the antibody of claim 19, wherein the antibody is a monoclonal antibody in a therapeutically effective amount sufficient to stimulate target cell differentiation in the presence of a sufficient amount of a differentiation inducing agent.

64. The pharmaceutical composition of claim 63, further comprising:

(a) a therapeutically effective amount of a differentiation inducing agent selected from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachinodate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivative, hormones, hormone antagonisits, and biologic promotors of differentiation, and derivatives thereof; and

(b) a pharmaceutically acceptable carrier.

65. The pharmaceutical composition of claim 63, wherein the differentiation inducing agent is HMBA.

66. The pharmaceutical composition of claim 63, wherein the monoclonal antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

67. A pharmaceutical composition comprising an antibody selected from the group consisting of: an antibody that specifically binds to Notch, or a portion of the antibody containing a binding domain thereof, or a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

68. The antibody of claim 19, wherein the antibody is a monoclonal antibody and the target cell is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

69. A polyclonal antibody generated against biologically active human Notch-1 EGF-repeats 11 and 12 that recognizes an extracellular epitope of Notch-1 and induces differentiation

of a tumor cell that overexpresses Notch-1, such that when differentiation of the tumor cells is induced, exposure of the cell to the polyclonal antibody induces apoptosis of the cell.

70. The polyclonal antibody of claim 69, wherein the biologically active human Notch-1 EGF repeats 11 and 12 is not reduced to cleave a disulfide bond.

71. A hybridoma that secretes any of the antibodies of claim 19.

72. The method of claim 1, further comprising treating the target cell with a therapeutically effective amount of another antineoplastic agent at a time that enhances apoptosis in the target cell.

73. The method of claim 72 wherein the other antineoplastic agent comprises vinca alkaloid.

74. The method of claim 73 wherein the vinca alkaloids are selected from the group consisting of vinblastine, Paclitaxel and vincristine.

75. The method of claim 72, wherein the antineoplastic agent is administered substantially concurruently with the agent administered to inhibit a cell fate determining function of a Notch protein in the target cell at a time when the cell is undergoing differentiation, which induces the target cell to undergo apoptosis.

76. A method of inducing apoptosis in a tumor cell that is characterized by increased expression of a Notch protein, comprising:

administering a therapeutically effective amount of a first antineoplasic agent to a subject having a tumor; and

interfering with the Notch function or expression in the cells of the tumor, at a time during differentiation when the Notch is required to prevent apoptosis, by administering a molecule that specifically interferes with the Notch function or expression at a time that enhances an effect of the first antineoplastic agent.

77. The method of claim 76, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch protein.

78. The method of claim 76, wherein administering the molecule comprises administering an antibody which specifically binds to the Notch protein and interferes with Notch function.

79. The method of claim 76 where in the tumor is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.